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Congress Must Fix the Inflation Reduction Act Before Millions Lose Treatment for Rare Diseases

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ABSTRACT

In 1983, Congress enacted the Orphan Drug Act (ODA) to incentivize new treatments for rare diseases, called "orphan drugs." The U.S. Food and Drug Administration (FDA) has approved over 700 new orphan drugs using these incentives. However, a poorly drafted section of the Inflation Reduction Act (IRA), which passed last year, is undoing them and may deprive millions of new treatments. This article describes the problem and some potential solutions.

INTRODUCTION

A rare disease is one that has fewer than 200,000 cases in the United States.[1] Over 10,000 rare diseases affect nearly 30 million Americans, and only about 5% have treatments approved by the FDA.[2] Most rare diseases

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1. 21 U.S.C. § 360bb(a)(2).

2. *Public Health Challenges of Rare Diseases*, NAT'L INST. OF HEALTH (NIH) GENETIC AND RARE DISEASES INFO. CTR. (June 9, 2023), https://rarediseases.info.nih.gov [https://perma.cc/3K78-S54A]; *Orphan Drugs in the United States: An Examination of Patents and Orphan Drug Exclusivity*, NAT'L ORG. FOR RARE DISORDERS (NORD) 4 (Oct. 2022), https://rarediseases.org/wp-content/uplo

are life threatening, and half of the affected patients are children.[3] According to the FDA, "Orphan drugs are desperately needed by patients with rare diseases."[4]

The ODA makes financing these drugs possible. The Act provides crucial financial incentives for orphan drugs such as a 25% tax credit for research and a seven-year delay before the FDA can approve a competing generic or biosimilar (called "orphan exclusivity").[5] The exclusivity allows an orphan drug manufacturer to recoup the average $1.5 billion dollar cost of bringing a new drug to market.[6]

The IRA threatens to undermine these incentives. The new law seeks to radically lower drug costs by imposing price controls on Medicare. These controls will have far-reaching effects on payments by private insurers and funding for rare disease research as well.

Congress anticipated the potential damage to orphan drug development and exempted "Certain Orphan Drugs" in section 1320f-1(e)(3)(A) of the IRA. But the exemption is ambiguous, and uncertainty about which drugs qualify is already chilling the development of new treatments.

Congress could fix the problem with minor changes to the exemption. However, this is unlikely to occur before at least 2026, when a federal study of orphan drugs will be completed. In the meantime, the Center for Medicare and Medicaid Services (CMS) can help by allowing orphan drug manufacturers to withdraw potentially disqualifying orphan designations. Manufacturers may also be able to sidestep the problem temporarily by submitting a separate application to the FDA for each new orphan designation.

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ads/2022/10/NORD-Avalere-Report-2021_FNL-1.pdf [https://perma.cc/6XBA-FBM8].

3. *Rare Diseases: Common Issues in Drug Development*, U.S. FOOD & DRUG ADMIN. 19 (Jan. 2019), https://www.fda.gov/media/119757/download [https://perma.cc/XM6P-FXTD].

4. *FDA/CDER Small Business Chronicles: Orphan Drugs*, U.S. FOOD & DRUG ADMIN. 1 (July 13, 2012), https://www.fda.gov/media/83372/download [https://perma.cc/GCV3-XL5A].

5. 26 U.S.C. § 45C; 21 U.S.C. § 360cc(a).

6. Olivier Wouters, Martin McKee & Jeroen Luyten, *Estimated Research and Development Investment Needed to Bring a New Medicine to Market 2009-2018*, 323 J. AM. MED. ASS'N 844, 844 (2020).

I. THE ORPHAN DRUG ACT MAKES TREATING RARE DISEASES ECONOMICALLY VIABLE

The FDA must designate a drug as an orphan drug to qualify it for the ODA's incentives. Orphan designation occurs in early phases of development when the manufacturer has little data, including whether the drug will succeed in clinical trials. To obtain designation, the manufacturer must provide only a "medically plausible basis" that the drug can safely and effectively treat a rare disease.[7]

Orphan designation is an important milestone toward FDA approval. While only about 1 in 10,000 potential drugs are approved by the FDA[8], the chances of approval rise to 17% when a drug receives orphan designation.[9] An almost equal portion of orphan designated drugs (15%) are withdrawn.[10] Some of the remaining products are still being developed, but the majority are abandoned either because the drug failed or the sponsor ran out of funding.

The ODA's incentives have been successful. Before the ODA was enacted in 1983, the FDA approved only 38 orphan drugs.[11] It has approved over 700 new orphan drugs since the ODA became law.[12]

However, there have been some complaints regarding the abuse of orphan designation. For example, a widely cited report by National Public Radio in 2017 focused on 80 drugs that were "repurposed" from mass-market indications to treat rare diseases. The investigation claimed that large companies sought orphan designation for blockbuster drugs to obtain

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7. 21 C.F.R. § 316.25(a)(2).

8. Jim Hahn, Kevin J. Hickey, Suzanne M. Kirchhoff & Hannah-Alise Rogers, *Selected Issues in Pharmaceutical Drug Pricing*, CONG. RSCH. SERV. 1 (Mar. 1, 2023), https://crsreports.congress.gov/product/pdf/IF/IF12272 [https://perma.cc/3VB8-VRHW].

9. Orphan Drug Designations and Approvals, OPD Listing U.S. FOOD & DRUG ADMIN. (last visited May 5, 2023), https://www.accessdata.fda.gov/scripts/opdlisting/oopd (1,173 approved orphan drugs out of 6,887 designations).

10. *Id.* (1,057 of 6,887 orphan designations were withdrawn).

11. NORD, *Orphan Drugs in the United States*, *supra* note 2, at 5.

12. Kathleen L. Miller, Lewis J. Fermaglich & Janet Maynard, *Using Four Decades of FDA Orphan Drug Designations to Describe Trends in Rare Disease Drug Development: Substantial Growth Seen in Development of Drugs for Rare Oncologic, Neurologic, and Pediatric-Onset Diseases*, 16 ORPHANET J. RARE DIS. 265, 268 (2021).

orphan exclusivity, delay competition, and keep prices high.[13] These criticisms focus only on a small portion of orphan drugs that do not accurately represent the sector.

Orphan drugs do often cost more, mostly because they do not benefit from economies of scale. 60% of orphan drugs treat only one rare disease, and their market is limited to at most 200,000 patients.[14] Typically, the rarer the disease the higher the cost because the expenses of development and manufacturing are divided among fewer purchasers.[15]

In addition, 85% of orphan drugs are developed by small, emerging companies.[16] These companies enjoy an average 8.8% increase in stock price after they receive orphan designation.[17] Medium and large companies do not receive this benefit.[18] More than anything else, orphan designation gives small companies the capital they need to keep going through clinical trials to FDA approval. That is precisely what the ODA intends.

II. THE INFLATION REDUCTION ACT MAY REDUCE DRUG PRICES BY 80%

On August 16, 2022, President Biden signed the IRA into law. The Act establishes far-reaching price controls for Medicare, including a requirement that drug manufacturers negotiate a "maximum fair price" with the Center for Medicare and Medicaid Services (CMS) for drugs

13. Sarah Jane Tribble & Sydney Lupkin, *Drugs For Rare Diseases Have Become Uncommonly Rich Monopolies* NAT'L PUB. RADIO (Jan. 17, 2017), https://www.npr.org/sections/health-shots/2017/01/17/509506836/drugs-for-rare-diseases-have-become-uncommonly-rich-monopolies [https://perma.cc/P94L-RAFV].

14. *Orphan Drugs in the United States*, IQVIA INST. 14-16 (Dec. 2020), https://www.iqvia.com/insights/the-iqvia-institute/reports/orphan-drugs-in-the-united-states-rare-disease-innovation-and-cost-trends-through-2019 [https://perma.cc/K422-WUU7].

15. *Id.*

16. David Thomas & Chad Wessel, *2019 Emerging Therapeutic Company Trend Report*, BIOTECHNOLOGY INNOVATION ORG. 40, https://go.bio.org/rs/490-EHZ-999/images/BIO%202019%20Emerging%20Company%20Trend%20Report.pdf [https://perma.cc/SX8Q-WN2L].

17. Kathleen L. Miller, *Do Investors Value the FDA Orphan Drug Designation?*, 12 ORPHANET J. RARE DIS. 114, 116 (2017), https://doi.org/10.1186/s13023-017-0665-6.

18. *Id.*

covered by the program.[19] CMS and drug manufacturers began price negotiations for the first 10 drugs on October 3, 2023.[20]

The price controls apply to "single source" drugs that have been approved for at least seven years and biologics approved for at least 11 years.[21] The IRA sets a timetable that CMS should negotiate prices for 10-20 drugs a year with the highest annual Medicare spending.[22] Some experts predict CMS will eventually require price controls for all drugs covered by Medicare.[23]

The IRA's maximum fair prices will be as much as 80% lower than current Medicare prices.[24] Since a rare disease is defined as one that affects fewer than 200,000 U.S. patients, a price reduction of this magnitude would make many orphan drugs a losing investment. But the IRA offers no choice. A manufacturer that refuses to agree to Medicare's maximum fair price may be charged an escalating "excise tax" between 185% and 1,900% of the drug's daily revenues, causing potentially millions in daily fines.[25]

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19. 42 U.S.C. § 1320f-2(a).

20. *Biden-Harris Administration Moves Forward with Medicare Drug Price Negotiations to Lower Prescription Drug Costs for People with Medicare*, U.S. DEP'T. OF HEALTH & HUM. SERV. (Oct. 3, 2023), https://www.hhs.gov/about/news/2023/10/03/biden-harris-administration-moves-medicare-drug-price-negotiations-lower-prescription-drug-costs-people-medicare.html [https://perma.cc/Z2EX-9JLR].

21. "Single-source" means the products have no competing generic or biosimilar versions. *See* 42 U.S.C. § 1320f-1(e)(1).

22. 42 U.S.C. § 1320f-1(a)(2)-(4).

23. Amitabh Chandra, *IRA's Impact on Biopharma Innovation Vital Health*, MOSSAVAR-RAHMANI CTR. FOR BUS. & GOV'T (Dec. 2, 2022), https://www.hks.harvard.edu/centers/mrcbg/programs/growthpolicy/iras-impact-biopharma-innovation [https://perma.cc/4UZ2-T2DM].

24. *Inflation Reduction Act–Medicare Part D Redesign/Patient Out of Pocket Cap*, BIOTECHNOLOGY INNOVATION ORG. (Dec. 14, 2022), https://archive.bio.org/sites/default/files/docs/toolkit/BIO_IRA-PartD-Redesign_Factsheet_v2%20FINAL.pdf [https://perma.cc/VZN9-8TZM].

25. 26 U.S.C. § 5000D; MOLLY F. SHERLOCK ET AL., CONG. RSCH. SERV., R47202, TAX PROVISIONS IN THE INFLATION REDUCTION ACT OF 2022 (H.R. 5376) 4 (2022); Michael Erman & Bhanvi Satija, *Pfizer CEO Calls U.S. Drug Price Plan 'Negotiation with a Gun to Your Head*,' REUTERS (May 12, 2023), https://www.reuters.com/business/healthcare-pharmaceuticals/pfizer-pouring-covid-profits-into-cancer-battle-ceo-bourla-says-2023-05-11 [https://perma.cc/G3BJ-GQBZ] (explaining that the potential fines for refusing to agree to

The maximum fair prices set by CMS will have effects far beyond Medicare. State Medicaid programs follow a "best price" that sets Medicaid prices at the lowest available to any U.S. entity, including Medicare.[26] Many private insurers provide prescription drug coverage to Medicare Part D beneficiaries and will also look to the maximum fair prices for their non-Medicare subscribers.

III. THE IRA HAS AN AMBIGUOUS EXEMPTION FOR "CERTAIN ORPHAN DRUGS"

Congress exempted at least some orphan drugs from Medicare price controls. Section 1320f-1(e)(3)(A) of the IRA excludes "Certain Orphan Drugs" described as a "drug that is designated as a drug for only one rare disease or condition . . . and for which the only approved indication (or indications) is for such disease or condition."[27]

The exemption first appeared in a Senate Finance Committee markup of H.R. 5376, the bill that became the IRA. The Committee proposed to limit the orphan drug tax credit to pre-approval testing for the "first use or indication with respect to which a drug for a rare disease or condition is designated."[28] The section 1320f-1(e)(3)(A) exemption first appears in the same draft.[29]

Patient advocacy groups opposed limitations on the orphan drug tax credit, arguing that they would destroy incentives for rare disease research.[30] As a result, the limitations were removed from H.R. 5376. However, the corresponding exemption for "Certain Orphan Drugs" remained, either intentionally or inadvertently. Neither provision was

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Medicare's maximum fair prices prompted one pharma company to describe the process as "negotiation with a gun to your head").

26. 42 C.F.R. § 447.505.

27. 42 U.S.C. § 1320f-1(e)(3)(A).

28. STAFF OF S. COMM. ON FIN., 117TH CONG., UPDATED BUILD BACK BETTER TEXT 881 (Comm. Print 2021), https://www.finance.senate.gov/imo/media/doc/12.11.21%20Finance%20Text.pdf [https://perma.cc/X5YT-XKC3].

29. *Id.* at 1028.

30. *Statement on Passage of the Inflation Reduction Act*, NAT'L ORG. FOR RARE DISEASES (NORD) 2 (Aug. 12, 2022), https://rarediseases.org/wp-content/uploads/2022/08/Reconciliation-Release-_-Aug-2022.pdf [https://perma.cc/SF3F-3PWE].

considered by the Senate Health Committee, which has primary expertise in pharmaceutical regulation.[31]

The intent of section 1320f-1(e)(3)(A) isn't clear. It seems intended to protect true orphan drugs—those that only treat rare diseases—but to limit orphan designation by "repurposed" drugs. For example, an existing mass-market drug seeking orphan designation years after approval would be subject to price controls, but a drug approved solely to treat rare diseases would be exempt.

However, the use of "designated" in the phrase "designated as a drug for only one rare disease or condition" is problematic. Since orphan designation occurs early on, manufacturers have limited data to predict a drug's effectiveness for a rare disease. The IRA's disallowance of more than one designation means a drug has no second chances with a new or modified designation, turning an orphan drug into a single, billion-dollar "all or nothing" bet with only a 17% chance of success.[32]

IV. Uncertainty About the Exemption is Chilling New Treatments

In a recent letter to CMS, 101 patient advocacy groups, led by the National Organization for Rare Disorders, warned that the IRA, as written, will destroy financial incentives for rare disease research.[33] They cautioned that imposing price controls on drugs with more than one orphan designation "will disincentivize drug companies from conducting even the basic research necessary to develop a drug for additional rare diseases."[34]

Medicare doesn't expect the first maximum fair prices to take effect until 2026, but uncertainty is already chilling the development of new treatments. Two manufacturers—Alnylam Pharmaceuticals and Eli Lily—

31. *HELP Committee Posts Updated Build Back Better Text Ahead of Bipartisan Parliamentary Discussions*, U.S. Congress, S. Comm. on Health, Educ., Labor & Pensions (HELP) (Dec. 11, 2021), https://www.help.senate.gov/imo/media/doc/KIN21845.pdf [https://perma.cc/2ZAR-VYA9].

32. Orphan Drug Designations and Approvals, note 9 above, at id.

33. Letter from 101 Rare Disease Patient Groups to the Ctr. for Medicare & Medicaid Services 3 (Apr. 14, 2023), https://rarediseases.org/wp-content/uploads/2023/04/FINAL_Rare-Disease-Patient-Organization-Sign-On-Letter-to-CMS-on-MDPNP-4.14.23-1.pdf [https://perma.cc/E7U2-T48K].

34. *Id.*

recently halted trials of new orphan drugs, citing uncertainty stemming from the IRA.[35]

An economic analysis for the Biotechnology Innovation Association predicts that because of IRA price controls, 40% fewer new drugs will come to market by 2035, including a loss of 14 new orphan drugs.[36] Dr. Amitabh Chandra, a researcher at Harvard University and an economic adviser to the Congressional Budget Office (CBO) explained, "the CBO has almost definitely understated the number of medicines that will not come to market as a result of the IRA."[37]

Council for Affordable Health Care—a coalition of health insurers and drug manufacturers—offered an even more dire prediction, writing, "[i]ntentionally or by mistake, the IRA makes clear that companies developing orphan drugs are now at increased risk of market failure—the opposite of what the Orphan Drug Act sought to address . . . . Many patients can say goodbye to hope as a result."[38]

V. CONGRESS AND CMS MUST ACT BEFORE MILLIONS LOSE TREATMENT

A. Congress Should Amend the IRA to Clarify the Orphan Drug Exemption

The only permanent solution to the uncertainty in orphan drug development is for Congress to clarify the section 1320f-1(e)(3)(A) exemption. A simple fix would be to delete the single designation requirement by removing "one" and making "rare disease or condition" plural. The existing text reads:

35. Joe Grogan, *The Inflation Reduction Act Is Already Killing Potential Cures*, WALL ST. J. (Nov. 3, 2022), https://www.wsj.com/articles/the-inflation-reduction-act-killing-potential-cures-pharmaceutical-companies-treatment-patients-drugs-prescriptions-ira-manufacturers-11667508291 [https://perma.cc/BUZ2-Z3BF].

36. *IRA's Impact on the U.S. Biopharma Ecosystem*, VITAL TRANSFORMATION 15 (Jun. 1, 2023), https://vitaltransformation.com/2023/05/iras-impact-on-the-us-biopharma-ecosystem [https://perma.cc/DHX6-BAYJ].

37. *Id.*

38. *How The Inflation Reduction Act Is Impacting Rare Disease Patients*, COUNCIL FOR AFFORDABLE HEALTH COVERAGE (Mar. 1, 2023), https://www.cahc.net/newsroom/2023/3/1/how-the-inflation-reduction-act-is-impacting-rare-disease-patients [https://perma.cc/E3PQ-WVZU].

> A drug that is designated as a drug for only one rare disease or condition under section 360bb of title 21 and for which the only approved indication (or indications) is for such disease or condition.

This would change to:

> A drug that is designated as a drug for only rare diseases or conditions under section 360bb of title 21 and for which the only approved indication (or indications) is for such diseases or conditions.

This change would preserve the exemption's apparent intent. True orphan drugs that are designated and approved only for rare diseases would be exempt from price controls, regardless of how many designations and approvals they received. However, any drug not orphan designated or approved for any non-orphan indication, such as a repurposed mass-market drug, would be subject to price controls.

Unfortunately, Congress is unlikely to make this or any other changes to section 1320f-1(e)(3)(A) until at least 2026. Another recent law, the Food and Drug Omnibus Reform Act of 2022, requires the Department of Health and Human Services and the General Accounting Office to conduct a detailed study of orphan drugs, notice the study for public comment, and report the results to Congress by September 2026.[39]

B. CMS Can Interpret the IRA to Exclude Withdrawn Orphan Designations

In their April 2023 letter, the 101 patient groups asked CMS to help reduce economic uncertainty about orphan drugs. They wrote, "[w]e urge CMS to clarify that obtaining additional designations for a small molecule or biologic will not make a drug negotiation eligible until the drug has been approved by the FDA to treat a second rare disease or solution."[40]

Current CMS guidance sheds little light on section 1320f-1(e)(3)(A).[41] However, the agency has suggested it might further clarify the statute,

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39. Consolidated Appropriations Act, 2023, Pub. L. No. 117-328, § 3202, 136 Stat 4459 (2022).

40. Letter from 101 Rare Disease Patient Groups, *supra* note 31, at 3.

41. *Medicare Drug Price Negotiation Program: Initial Memorandum, Implementation of Sections 1191–1198 of the Social Security Act for Initial Price Applicability Year 2026, and Solicitation of Comments*, CTR. FOR MEDICARE & MEDICAID SERVICES 10 (Mar. 15, 2023), https://www.cms.gov/files/document

stating, "CMS is considering whether there are additional actions CMS can take in its implementation of the Negotiation Program to best support orphan drug development."[42]

One action CMS could take is to interpret the IRA as excluding withdrawn orphan designations. FDA regulations permit a sponsor to withdraw orphan designation "at any time after the request is submitted or granted, respectively, by submitting a written request for withdrawal to FDA."[43]

A clear statement from CMS that a withdrawn designation won't count against the designated for "only one rare disease" limitation in section 1320f-1(e)(3)(A) could significantly bolster investor confidence in orphan drugs. It would transform orphan drug development from an "all or nothing" bet to a sequential approach. Interested parties could petition CMS for new or revised guidance permitting the withdrawal of orphan designation.[44]

C. Manufacturers Might Use Multiple Applications as a Short-Term Workaround

Orphan drug manufacturers may also be able to sidestep section 1320f-1(e)(3)(A)'s limitations by dividing new orphan drugs into multiple applications for FDA approval. A manufacturer could submit multiple investigational new drug applications (INDs) for the same drug, each seeking a single orphan designation. If pursued to its logical end, this process could yield multiple approved drugs with the same active ingredient, each designated and approved to treat only a single rare disease within the exemption.

The FDA would require a manufacturer to divide a drug into multiple applications if there are significant quantitative or qualitative differences among its different versions, called "presentations."[45] For example, the FDA

/medicare-drug-price-negotiation-program-initial-guidance.pdf [https://perma.cc/7LEZ-9KFH].

42. *Id.*

43. 21 C.F.R. § 316.24(d) (2023).

44. 45 C.F.R. § 1.5 (2023).

45. *Guidance for Industry–Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*, U.S. FOOD & DRUG ADMIN (FDA) 3 (Dec. 2004), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submitting-separate-marketing-applications-and-clinical-data-purposes-assessing-user-fees [https://perma.cc/X2KF-NVKA].

would mandate separate applications if one presentation of the drug is administered by injection and another by pill.

Sometimes, manufacturers opt for multiple applications for strategic reasons. In a joint venture, one company may own the rights to use the drug for one disease, while a second company owns separate rights to use the drug for another disease.[46] Developing the drug through separate applications allows each company to control one application, providing both with greater flexibility in marketing, licensing, pricing, and other operations.

But using multiple applications is an expensive, short-term solution at best. According to one estimate, each additional application for the same orphan drug would cost an additional $150 million.[47] The second application is also likely to forfeit regulatory exclusivity that it would otherwise receive for a new drug or biologic.[48] Ironically, these hardships are more easily borne by a large company repurposing a mass-market drug than by an emerging company is seeking FDA approval for an entirely new one.

CONCLUSION

Pricing orphan drugs is less a crusade against greedy pharmaceutical companies than a balancing act among scientific uncertainty, patient care, and scarce resources. For every drug that is approved by the FDA, few see the thousands that failed.

The ODA's incentives have balanced the scales for decades. Now, the IRA threatens to smash them. Congress must reduce uncertainty and restore investor confidence in orphan drugs. We will never know how many cures we have lost until it does.

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46. For example, the drugs Eyelea (Aflibercept) and Zaltrap (Ziv-afilbercept) contain the same active ingredient developed in a joint venture between Regeneron and Sanofi Aventis. Eyelea treats several eye diseases while Zaltrap treats colorectal cancer. *See, e.g.*, Drugs@FDA: FDA-Approved Drugs, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm (last visited: Jun. 15, 2023) [https://perma.cc/AJ3A-W4LS].

47. *IRA's Impact on the U.S. Biopharma Ecosystem*, *supra* note 33, at 25.

48. New small molecule drugs receive five years of New Chemical Entity exclusivity. New biologics receive 12 years of Reference Product Exclusivity. 21 U.S.C. §§ 355(c)(3)(E)(ii) & (j)(5)(F)(ii); 42 U.S.C. § 262(k)(7)(A).